



NTP
National Toxicology Program

NTP Board of Scientific Counselors

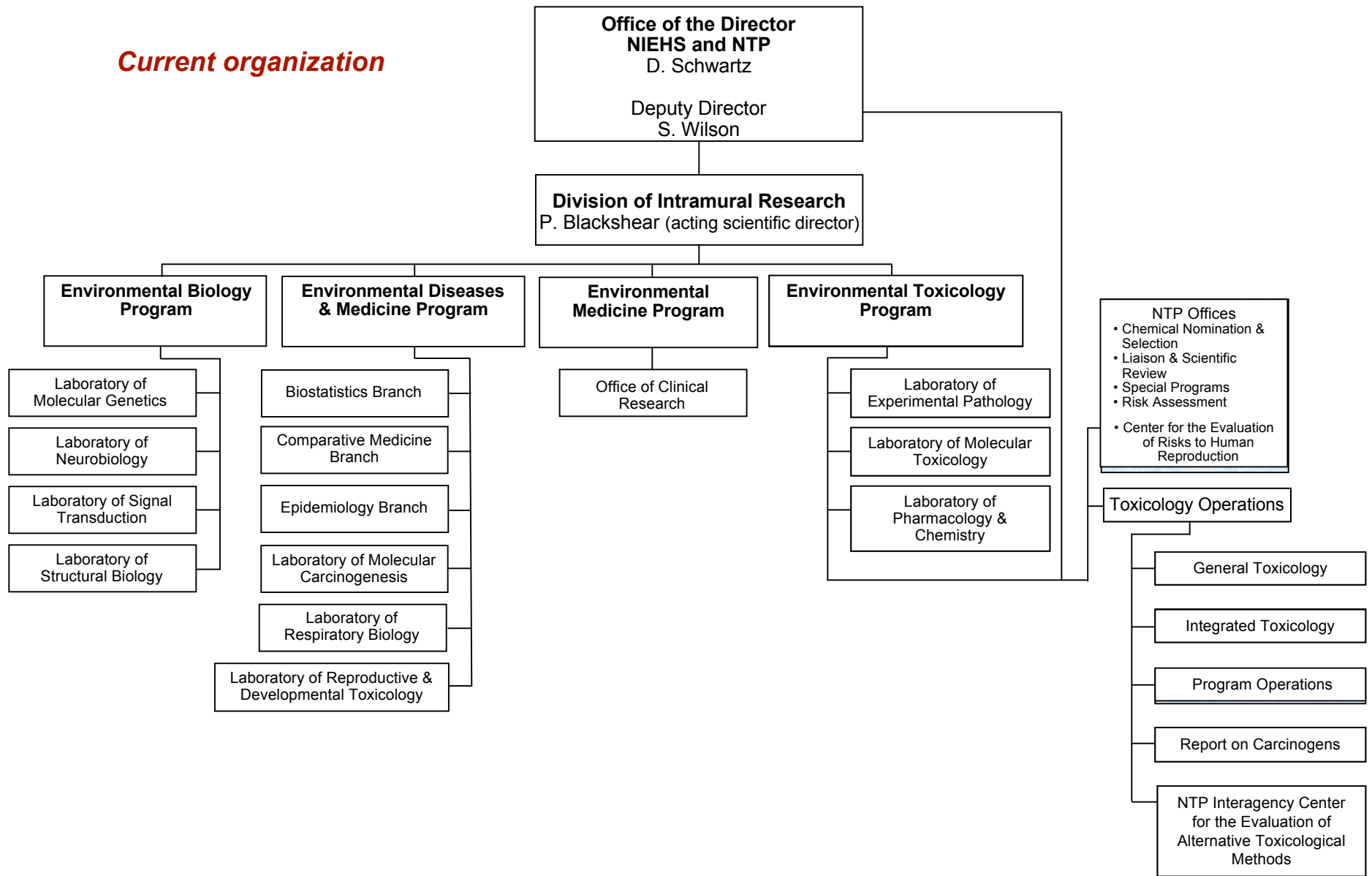
NTP Update

John R. Bucher, Ph.D.
June 22, 2007



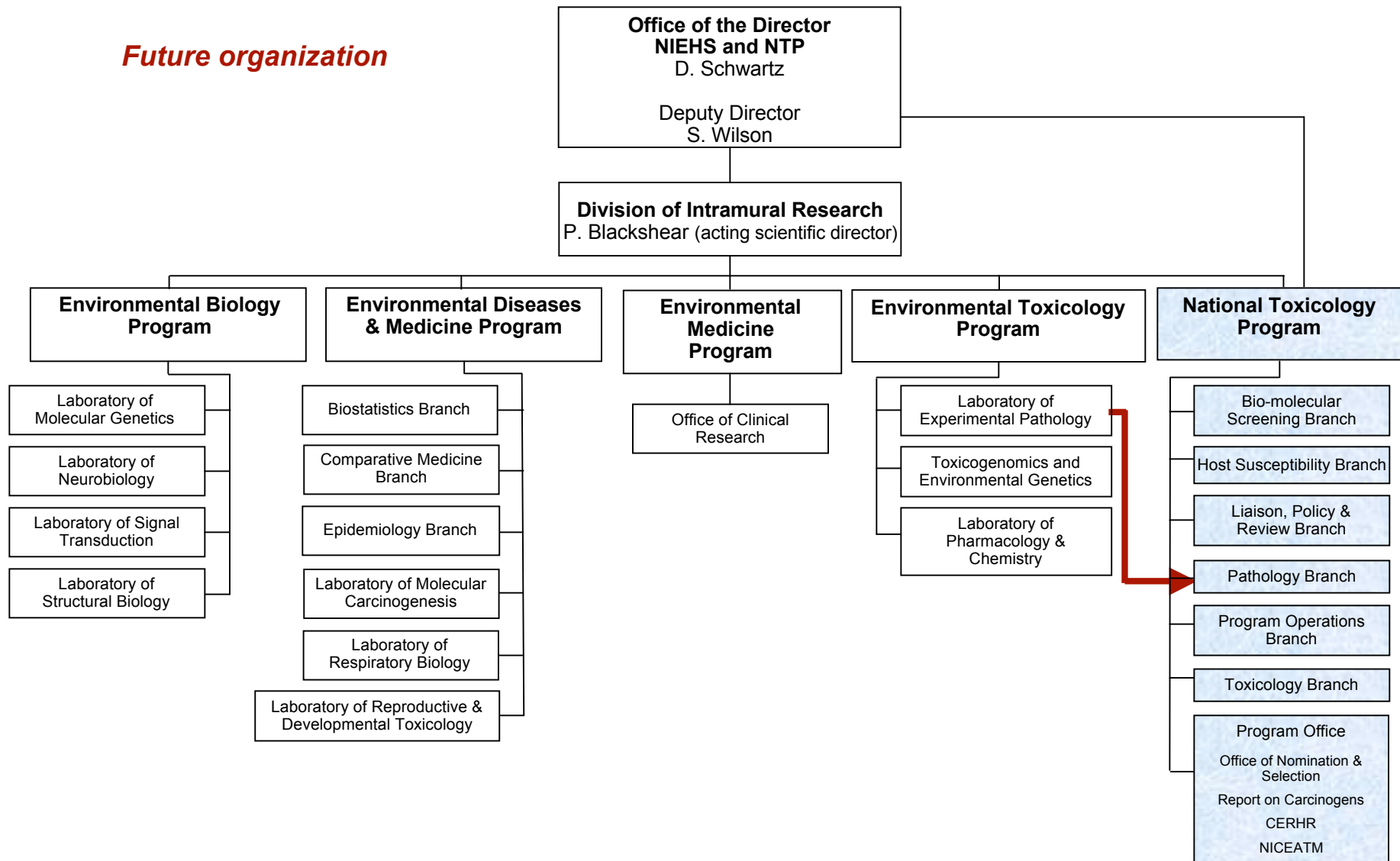
Division of Intramural Research

Current organization



Division of Intramural Research

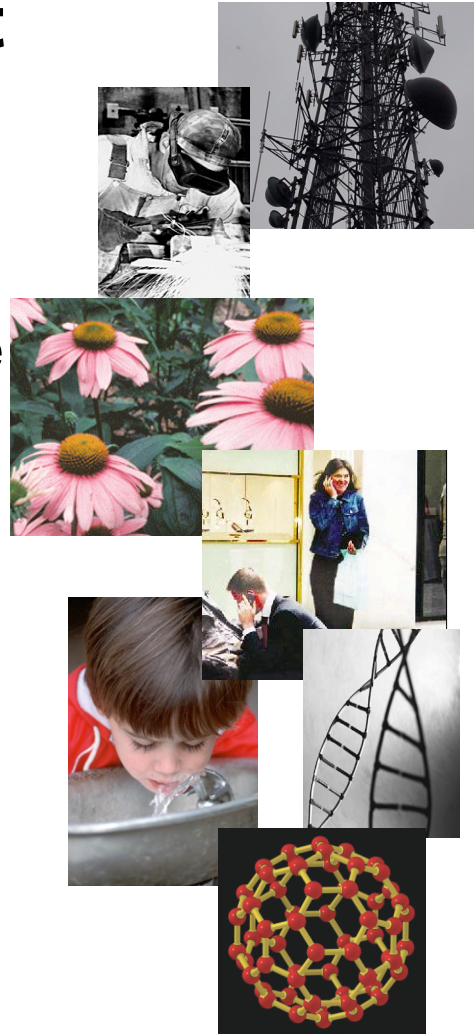
Future organization





Rationale for Program Realignment

- Provides an identifiable home
- Brings analysis activities into Program Office
- Creates structure for program development
- Allows for staff accountability
- Allows for budget accountability
- Maintains scientific integration within DIR



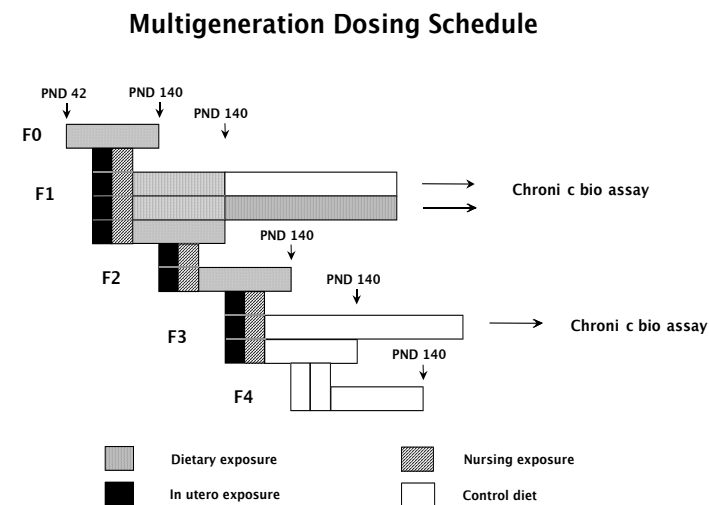


NTP Technical Reports Highlights

TR Subcommittee Meeting, May 16-17, 2007

- Sodium Dichromate Dihydrate (hexavalent chromium) drinking water studies
 - Squamous cell papillomas and carcinomas of the oral mucosa- rats
 - Adenomas and carcinomas of the small intestine- mice
- Ethinyl Estradiol (multigeneration and cancer) feed studies
 - Continuous exposure suppressed body weights, and accelerated puberty and perturbed estrous cycles in females. Mammary gland hyperplasia occurred in continuously exposed males.
 - No convincing evidence of carry over of effects into unexposed generations
 - Equivocal evidence of carcinogenic activity in male and female rats exposed to EE in the various F1 and /or F3 exposure arms

TR Subcommittee will report to full BSC
at next meeting





NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) Update

- 1st expert panel meeting on Bisphenol A- March 5-7, 2007
 - Allegations of potential conflict of interest with support contract
 - Review all NTP contracts for potential for COI
 - Develop COI language to incorporate in all NTP contracts
 - Audit the literature search/selection for the preliminary draft of the BPA expert panel report
 - Audit the fidelity of changes to the December and March versions of the expert panel report
- 2nd expert panel meeting on Bisphenol A- August 6-8, 2007
- Genistein and soy formula NTP Briefs are in revision following public comment.
- Hydroxyurea Brief in preparation



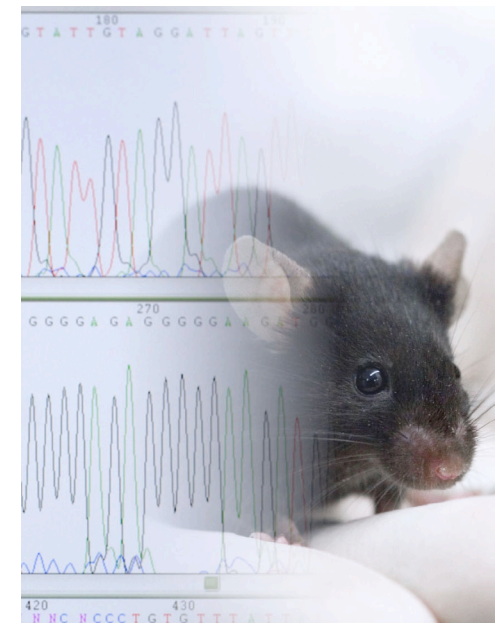
Nominations Update

- Office of Nominations and Selection in Program Office
- Dr. Scott Masten heads effort
- Central review and distribution site for all nominations
- Nomination reviews modified to increase opportunity for public comment
- Use of ad hoc reviewers
- Presentation of initial research concepts by program staff



Host Susceptibility Initiative

- Study the genetic basis underlying biological response
- Utilize multiple strains of inbred mice or GMMs
- Distinguish genetic from kinetic differences in response
- Exploit findings from NTP 15 isogenic mouse strain SNP analysis (> 8 million SNPs)
- Provide data to allow identification of QTLs with selected biological responses
- Partner with intramural and extramural scientists



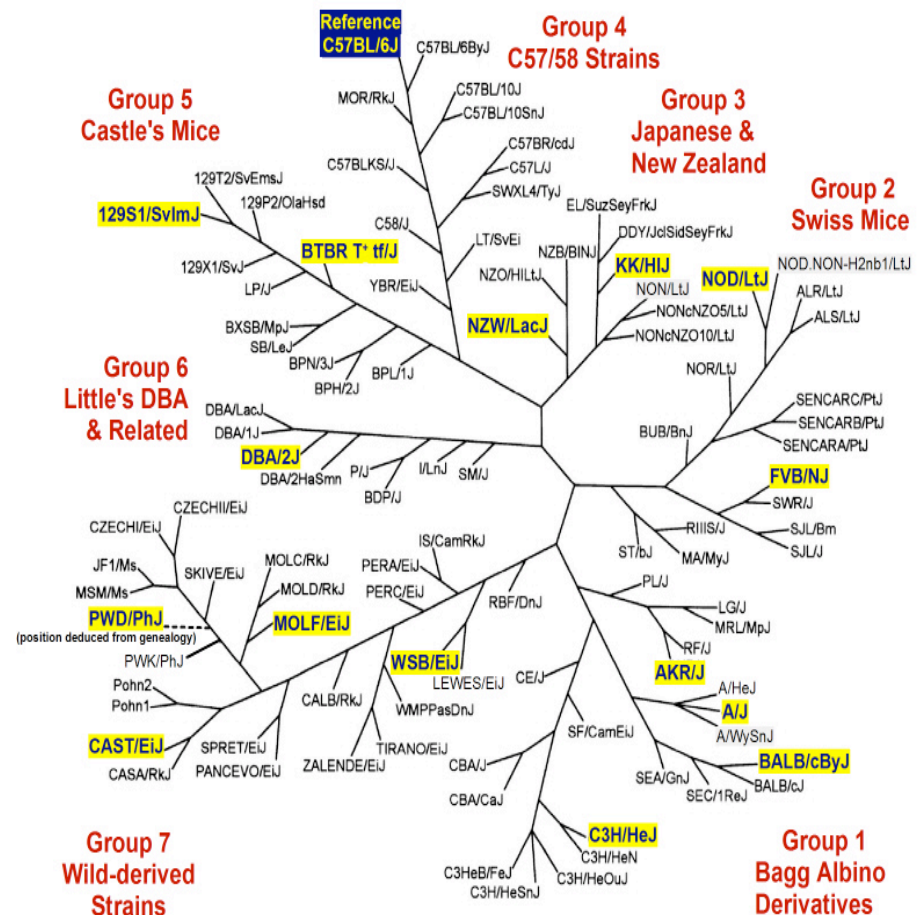


Host Susceptibility Initiative Update

- Host Susceptibility Branch created in NTP realignment
- Dr. Jef French appointed acting Chief
- Contract concept reviewed by BSC in Dec. 2006
- Current thinking on involvement of research partners
 - Program patterned after NCI RAID program (Rapid Access to Intervention Development)
 - Projects proposed by academic, government, or possibly other entities
 - Reviewed by “study section” arranged by NTP, and by NTP staff
 - Studies carried out by NTP utilizing NTP contracts and resources
 - Study materials/data made available for analysis by partners
 - No funding provided by NTP to research partners

Environmental Airway Disease Project

- Supporting the Gene and Environment Initiative
- Utilize inbred strains of mice to study genes involved in airway disease and identify biomarkers of response
- LPS, ozone, cigarette smoke, house dust mite allergen
- 15 strains of inbred mice
- Acute (one day) and chronic studies (~ 5 weeks)
- Immediate and delayed endpoint measures
- Pulmonary function
- Lung tissue- histopathology, RNA
- BAL
- Cell differentials
- Cytokines
- Immune measures on spleen
- Tissues available for collaborators





NTP-HTS Molecular Libraries Initiative

- NTP became a formal participant in the NIH Molecular Libraries Initiative (MLI) in August 2005.
- The MLI – a part of the NIH Roadmap for Medical Research – uses automated screening methods to identify small molecules that can be used as chemical probes to study the functions of genes, cells, and biochemical pathways.
- The NTP, in conjunction with the MLI, will generate information that can link data on the biological activity of environment substances with toxicity endpoints identified in the NTP's toxicology testing program.



High-Throughput Screening Update

- NIH Chemical genomics Center has over 100 automated HTS assays available
- The NTP 1408 have been assayed in 14-pt dose response curves in:
 - cytotoxicity assay (CellTiter Glo) in 9 human and 4 rodent cell types
 - caspase 3,7 assays in 6 human and 3 rodent cell lines
 - Cytotox-One (LDH release) in 1 human and 1 rodent cell line
- Plans including running the 1408 in approximately 60 assays including cell signaling, DNA repair, Hsp90 interactions and other biological activities



High-Throughput Screening Update

- Establishing an IAG with NCGC
- Developing a second set of 1408 chemicals
- Identifying assays specifically focusing on immunotoxicity and cancer
- Presented 3 posters at SOT in March 2007
- Organized a symposium at the 2007 Annual Meeting of the Society for Biomolecular Sciences titled “Toxicity Profiling using High-Throughput and High Content Technologies”
- Continue to collaborate with EPA in the development of ToxCast



NICEATM/ICCVAM Update

- Five year plan report (Dr. Stokes)
- Current activities
 - *In vitro* endocrine disruptor screening methods
 - Refinements to *in vitro* ocular toxicity methods
 - Reviews of *in vitro* pyrogenicity methods
 - *In vitro* alternatives for testing vaccine efficacy, botulinum potency
- Expanded role in development of OECD guidance documents
 - OECD guidance documents on *in vitro* GLPs and validation process
- Continued global harmonization (ECVAM, JaCVAM)



NTP Goals

- Coordinate toxicological testing programs within the Department of Health and Human Services
- Strengthen the science base in toxicology
- Develop and validate improved test methods
- Provide information about potentially hazardous substances to health regulatory and research agencies, scientific and medical communities and the public



Program Strengths

- Located within NIH, physically and scientifically
- Recognized internationally as a leader in toxicology
- Perform both research and analysis activities
- Very talented staff dedicated to improving public health
- Team approach to solving problems
- Adequate budget
- Resources to address problems on a scale unequalled by others
- Expectations for excellence





Program Expectations

- Continue to provide basic toxicology information for public health protection
- Increase emphasis on understanding and explaining exposure-response relationships and genetic determinants of response
- Integrate results from new “data rich” techniques; genomics, proteomics, HTS screens with existing testing information
- Develop new methodologies for toxicological assessments
- Provide guidance for the proper utilization of new types of information in hazard identification, characterization and regulation